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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/779,767	01/07/97	ZAGHOUANI	H	ALLIA.143A

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EXAMINER	
REEVES, J	
ART UNIT	**PAPER NUMBER**
1642	15

DATE MAILED: 10/01/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/779,767	Applicant(s) Zaghouani
	Examiner Julie E. Reeves, Ph.D.	Group Art Unit 1642

☒ Responsive to communication(s) filed on *6/4/98 and 8/3/98*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *4-6, 9, 11-21, 24-27, 29-70, 72, and 73* is/are pending in the applicat

Of the above, claim(s) *5, 12-21, 25, and 30-65* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *4, 6, 9, 11, 24, 26, 27, 29, 66-70, 72, and 73* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *14*

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. As of February 7, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1642, Technology Center 1600.

2. Claims 66-73 have been added. Claims 1-3, 7-8, 10, 22, 23, 28 and 71 have been canceled. Claims -6, 9, 11, 24-27, 29, 68-69 and 72 have been amended. Claims 5, 12-21, 25 and 30-65 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected inventions, the requirement having been traversed in Paper No. 6. Claims 4, 6, 9, 11, 24, 26-27, 29, 66-70 and 72-73 will be examined to the extend that they read upon proteolipid protein.

3. The text of those sections of Title 35, U.S.C. Code not included in this Office action can be found in a prior Office Action.

Information Disclosure Statement

4. It is noted that Applicants have cited several references in the Woods Declaration submitted with their response filed 6/4/98. These references have not been made of record on a PTO 1449 and will not be cited on the face of the file once the application goes on to issue as a patent. Should Applicant wish to have these references made of record, it is suggested that Applicant file a PTO 1449 citing these references.

Claim Rejections - 35 U.S.C. § 112

5. The rejection of Claims 4, 6, 9, 11, 24, 26-27, 29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of the amendments to clarify the claims.

6. The rejection of Claims 9, 11 and 29 under 35 U.S.C. § 112, first and second paragraph, as the claimed invention is not described in such full, precise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the use of the term "chimeric" has been withdrawn in view of the amendments to remove the term "chimeric" from the claims and in view of the response set forth on page 6, of Paper no 11 filed 6/4/98.

7. The rejection of Claims 4, 6, 9, 11, 24, 26-27, 29 and newly added claims 66-70, 72-73 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention has been made again and maintained in part, as discussed below.

a. Concerning the maintenance of antigen binding properties, applicant's arguments set forth on pages 6-7 of Paper no 11 filed 6/4/98 are persuasive.

b. The rejection of claims 24 and 26-27, and 29 has been withdrawn in view of the amendment to delete the intended use term "pharmaceutical" from the first line. Applicant's arguments concerning FDA approval, citing In re Brana, throughout pages 7-14, is noted. The Examiner has not asked for FDA approval of the claimed composition. The enablement rejection set forth in the previous Office Action centered on the unpredictability of using the then-claimed pharmaceutical composition for treatment. Evidence of a reasonable correlation between the results obtained from studies conducted using animal models and those results expected to be obtained when the compositions were administered in a human would have been favorably considered. The declaration of Woods does not provide any such evidence. As stated by applicant, the claimed invention may be used in in vitro models for studying the presentation of antigens associated with autoimmune disease (page 11, past paragraph).

c. Concerning claims 4, 6, 9, 11, 24, 26-27, 29 and newly added claims 66-70 and 72-73, the fact remains that there is a great deal of art-recognized unpredictability in the area of immunosuppression via the endocytic presentation of T cell antagonists, as evidenced by Sercarx et al, Sebzda et al, Jameson et al, Livingstone et al, Jameson et al; Hsu et al; Feldman et al, Evavold et al and the abstract of Evavold et al were also relied upon in the previous Office Action for teaching various other examples of the unpredictability of modulating or suppressing the immune response with endocytically presented T cell peptides antagonists.

d. The response set forth on page 7-14 has been considered carefully but is deemed not to be persuasive. With regards to Sercarx et al, the response argues that because the claims no longer recite 'immunosuppression', the rejections no longer applicable. This is not persuasive, because knowing which peptides to use as T cell antagonists for endocytic presentation remains unpredictable. The response argues that the experimentation required would not be considered "undue" and cites In re Wands for support. This is not persuasive because the decision from In re Wands is not based on the same type of invention as that claimed. The fact situation of In re Wands involved screening hybridomas for the production of an antibody which bound a specific, well known antigen Hepatitis surface antigen, with a certain level of affinity. At the time of that claimed invention, the production of monoclonal antibodies was considered routine, the antigen was readily available, and one skilled in the art would reasonably expect to be able to identify an antibody with the claimed binding affinities. In this case, the claims, which are not limited to one target, broadly encompass "any T cell receptor antagonist" and propose using any peptide analogs. Screening for antigen- antibody interactions is simpler than screening for T cell receptor antagonists for the following reasons: antigen-antibody binding assays are routinely conducted in a cell free system and involve only the binding of an antigen to an antibody. Screening for T cell receptor antagonists involves the endocytosis and intracellular processing of peptide analogs, their presentation on the surface of T cells by one of the many MHC molecules present in the organism, and binding of the peptide-MHC complex to another cell presenting the TCR. When one skilled in the art compares an assay requiring two different cell types (APC and T cell) and four different

molecules (Ig-TCR antagonist, MHC Class II molecule, TCR and processed peptide) with the cell free assay highlighted in in re Wands, which requires only an immunoglobulin and its antigen, the level of experimentation required remains undue.

e. The response states that the specification describes methods for constructing , characterizing and determining the efficacy of claimed compositions. The fact remains that the specification has enabled the insertion of the specific PLP peptide analogs into the third CDR of the immunoglobulin heavy chain. The Declaration of Woods does not provide any other evidence or data of other T cell receptor antagonists which have been inserted into any different portions of an immunoglobulin.

f. The claims recite compositions comprising an immunoglobulin and T cell receptor antagonist peptide which has the property of being capable of endocytic presentation of T cell receptor peptide antagonists. One skilled in the art would reasonably conclude that the presentation and binding of the T cell antagonist shares common prerequisites as the presentation and binding of the T cell agonists in that they both must (1) be endocytically presented, (2) by MHC Class II and (3) bind to both MHC Class II and T cell receptor on the cell surface. Further, one skilled in the art would reasonably expect that thymic selection, which involves the binding of MHC class II presented peptides with a TCR, is comparable to the claimed composition which would bind an MHC Class II presented peptide with a T cell receptor. The response argues that the present invention relates to inhibition of activity of mature peripheral T cells. This is not persuasive because no such limitation can be found in the claims. Applicant is

reminded that the claims define the subject matter of his invention and that the specification cannot be relied upon to read limitations into the claims. Arguments presented that rely on particular distinguishing features are not persuasive where those features are not recited in the claims.

g. The response argues that Feldman indicates nonspecific T cell regulation, and the response describes the present application as a specific approach. It is not clear how an invention directed against any t cell receptor antagonist peptide analog could be considered "a specific approach". Applicant sates that they have demonstrated the claimed invention in a standard animal model, however, no evidence has been provided to demonstrate that the EAE mouse model of the instant application is a standard model and that results obtained from the mouse model would reasonably correlate with those expected in humans.

h. The response argues that Jameson supports the claimed invention by stating that "T cell response of less diversity...maybe very susceptible to antagonism". This is not persuasive because the broadly written claims are not limited to T cell responses of less diversity, whatever that may mean.

i. The response states that the Woods Declaration asserts that those skilled in the art would be able to select T cell antagonists. The response states that since the publication of Livingstone, numerous altered peptides which have been constructed and characterized. As evidence by the following reference newly provided by Applicant in support of their broadly claimed invention, their is art-recognized unpredictability concerning the production and use of

peptide analogs that function as T cell antagonists. For example, Bluestone et al (WO94/28027), recently provided in Paper no 14, teach that T cell activation is an unexpectantly complex phenomenon the depends on the participation of a variety of cell surface molecules expressed on the responding T cell population" (page 18, first full paragraph). Bluestone et al also teach that the MHC proteins represent another highly polymorphic set of molecules randomly dispersed throughout the species (pages 18-19 bridging paragraph). One skilled in the art would reasonably expect that any inhibition of the T cell activation, by anergy, suppression or by T cell antagonists, would also be inherently complex task in view of the complexity of the T cell system, as evidenced by Bluestone et al. With regards to T cell antagonist peptides, their is art-recognized unpredictability, as evidence, for example, by Sette et al, cited in the Woods Declaration. Sette et al clearly teach that "it is well known that for a given receptor, different ligands may exhibit antagonism and/or partial agonism to different degrees, depending for example on the affinity of the receptor. Therefore, depending upon the particular analog studied, it is possible the TCR engagement can be associated with either no activation, partial or full activation. The same ligands may also be classified as partial agonists or a pure antagonists, depending on the T cells and the nature of the APC. In fact we have observed that certain analogs can at low concentrations, behave as antagonists, whereas at higher concentrations, that have agonist activity. What is noteworthy is that all of the experimental systems described lead to a similar basic conclusion, viz. *Antigen analogs that are nonstimulatory for T cells as measured by proliferation assays can be shown to engage the T cell receptor in a biologically relevant*

function" (page 419, last paragraph, original emphasis). Sette et al emphasize that some antigen analogs may be able to act as both TCR antagonists and T cell tolergens" (page 420, last paragraph). Sette et al clearly state that no general rules could be formulated in the relationship between structure and activity of TCR antagonists (page 421, second full paragraph). Sette et al suggest that peptides with conservative substitutions tended to be powerful antagonists, while those with semiconservative or no conservative substitutions tended to be less potent antagonists or even no antagonists potential whatsoever. It would require one skilled in the art undue experimentation to determine the antagonistic properties of a peptide which contained conservative, semiconservative or non-conservative substitutions, because Sette et al teach that no general rules can be formulated.

j. Similarly, as evidenced by the following references newly provided by Applicant in support of their broadly claimed invention, the claimed invention involves art-recognized unpredictability concerning the production and use of peptide analogs that function as T cell antagonists. Hudrisier et al teach that single amino acid substitutions in MHC presented viral antigens result in dramatic functional properties (see Abstract). Further, Karin et al teach that "no single mutated peptide could antagonize the response of the majority of these PLP clones in vitro" and that peptides containing mutated TCR putative binding sites may display variable degrees of antagonism toward a collection of T cell clones with similar antigen specificity and MHC restriction (bridging paragraph pages 2234, col 1-2).

k. There is insufficient guidance in the specification as to how to determine which antagonists peptide or combination of antagonist peptides can be administered to any particular population of T cells for the function as a T cell antagonist. It appears that undue experimentation would be required of one skilled in the art to practice the instant claimed invention using the teachings of the specification. See Ex parte Forman, 230 USPQ 546 BPAI, 1986.

Claim Rejections - 35 U.S.C. § 103

8. Claims 4, 6, 9, 11, 24, 26-27, 29, 66-70 and 72-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kuchroo et; Mueller et al; in combination with WO 94/14847, Zanetti et al, US Patent 5,508,386; Kappler et al; Selick et al (WO 93/10220 3/93, PTO 1449 paper no 7) and Bona et al, for the reasons set forth in the previous Office Action. The claims have been amended to so they no longer recite an immunosuppressive agent and includes an intended use clause of "having the property of being endocytosed by cells bearing said Fc receptor and processed by the cells to present said T cell receptor antagonist in association with endogenous MHC Class II molecules". The fact remains that the claims recite an immunoglobulin molecule that incorporates a peptide comprising a T cell receptor antagonist.

a. The response set forth on page 14-17 has been considered carefully but is deemed not to be persuasive. The response argues that Kuchroo et al and Mueller et al which teach T cell

receptor peptide antagonists, fail to disclose linking the T cell receptor antagonist peptides to immunoglobulin peptides. In response, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

b. The response states that Zanetti et al, which discloses the insertion of foreign peptides into the third CDR of an immunoglobulin heavy chain, is primarily concerned with immunization and tolerization. The response argues that tolerance is mediated by a different population of cells. It is noted that a product and not a method of treatment are being claimed.

c. The response states that Bona et al "speculate" that is possible that the Ig bearing epitopes f self antigens will be more efficient for peptide competition therapy envisioned as a novel immunotherapeutic approach of autoimmune disease". Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company, Inc., 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

d. The response argues that Kappler et al and Selick et al do not provide an reasonable expectation of success because they fail to present experimental data that the compositions disclosed are effective in inhibiting an immune response. Applicant is reminded that

the claims define the subject matter of his invention and that the specification cannot be relied upon to read limitations into the claims. Arguments presented that rely on particular distinguishing features are not persuasive where those features are not recited in the claims.

e. With regards to paragraph 8 of the Declaration submitted under 35 U.S.C. 1.132, paper no 12 filed 6/4/98, Dr. Woods stresses the difference between tolerization and claimed invention. This is not persuasive in view of the fact that the claims recite products and not methods of treatment and further in view of the teachings of Sette et al (Ann Rev Immunol Vol 12:413-431, 1994, provided by Applicant as an attachment to the Woods Declaration) which states that "it should be emphasized....that some antigen analogs may be able to act as both TCR antagonists and T cell tolergens" (page 420, last paragraph).

f. The fact remains that is would have been obvious to have added the well known proteolipid protein peptide analogs to the third CDR of Zannetti et al's immunoglobulin to make the claimed product. The combination of references Kuchroo et; Mueller et al; WO 94/14847, Zanetti et al, US Patent 5,508,386; Kappler et al; Selick et al (WO 93/10220 3/93, PTO 1449 paper no 7) and Bona et al provide the motivation and reasonable expectation of success of obtaining the claimed composition which comprises an immunoglobulin linked to a proteolipid protein peptide analog. The composition would be capable of being endocytosed by cells bearing the Fc receptor, because Zannetti et al 's immunoglobulin contains the constant region involved with binding the Fc receptor. It is well known property of endocytosed antibodies that their antigens are processed by the cells and are presented on MHC Class II molecules and one skilled

in the art would reasonably expect that the endocytosed composition taught by the combination of the prior art would also be endocytosed, processed and presented in association with endogenous Class II molecules.

9. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action, particularly by citing newly submitted references which support the Examiner's position. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

13. All Internet e-mail communications will be made of record in the application file. **PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122.** This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie E. Reeves, Ph.D.

(703) 308-7553

SHEELA HUFF
PRIMARY EXAMINER